REMARKS

I. Status of the Claims

Claims 1-8 are withdrawn.

Claims 10, 11, 13 and 14 are amended.

Claims 16 and 17 are new.

Claims 9-17 are pending.

II. Interview Summary

Applicant thanks Supervisor Padmanabhan and Examiner Cotton for suggestions on claim amendments to move this case toward allowance. A question of total daily dosage as distinct from unit dose, e.g. dose per capsule, arose. Claim amendments with support from the specification were suggested, as long as the claim scope was not within the art, e.g. in Examples 1-46 in Caruso. Support for the daily doses and unit doses are found on at least the following locations. Citations are to paragraphs in the specification:

What is a "low dose" tricyclic antidepressant?

[00008] 25 mg/day or less.

[00010] 0.5 gm-2.6 gm daily; 0.5-2 gm/day acetaminophen; 0.6-2.6 gm/day aspirin; 0.6-1.8 gm/day ibuprofen.

What is the "standard dose" of non-narcotic analgesic?

[00011] 2.5 mg to 25 mg/day (.5 mg to 2 mg, 10-15 mg/day).

[00015] Example 1: 500 mg acetaminophen + 5 mg doxepin (unit dose).

[00016] Example 2: 5 mg doxepin + 650 mg aspirin, unit dose, twice daily.

[00017] Example 3: 10 mg doxepin + 600 mg ibuprofen.

The references requested by the examiner regarding low and standard doses are in Exhibits A and B.

No fees are believed due at this time, however, please charge any additional deficiencies or credit any overpayments to deposit account number 12-0913 with reference to our attorney docket number (41957/102748).

Respectfully submitted,

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Registration No. 35,601

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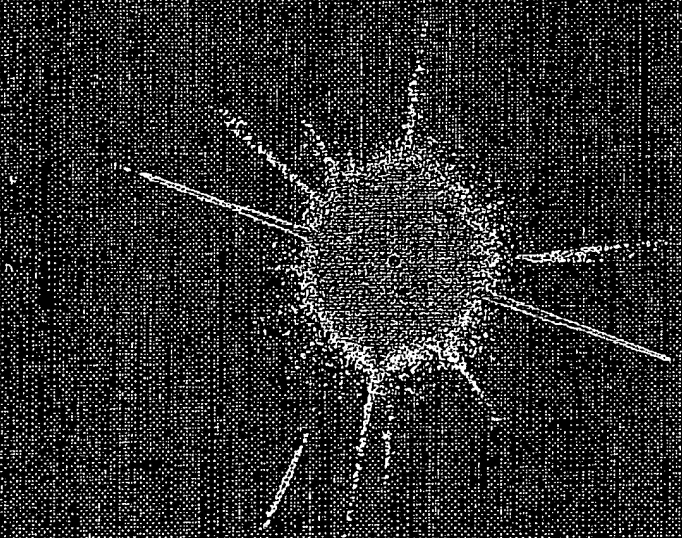

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Note: Dr. Fauci and Dr. Longo's works as editors and authors were performed outside the scope of their employment as U.S. government employees. These works represent their personal and professional views and not necessarily those of the U.S. government.

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The introduction of a parenteral form of NSAID, ketorolac, *extends the usefulness of this class of compounds in the management of acute severe pain. Ketorolac is sufficiently potent and rapid in onset to supplant opioids for many patients with acute severe head*ache and musculoskeletal pain.

Opioid Analgesics Opioids are the most potent pain-relieving drugs currently available. Furthermore, of all analgesics, they have the broadest range of efficacy, providing the most reliable method for rapidly relieving pain. Although side effects are common, except for respiratory depression, they are usually not serious and can be reversed rapidly with the narcotic antagonist naloxone. The physician should not hesitate to use opioid analgesics in patients with acute severe pain. Table 12-1 lists the most commonly used opioid analgesics.

Opioids produce analgesia by actions in the central nervous system. They activate pain-inhibitory neurons and directly inhibit pain-transmission neurons. Most of the commercially available opioid analgesics act at the same opiate receptor (mu receptor), differing mainly in potency, speed of onset, duration of action, and optimal route of administration. Although the dose-related side effects (sedation, respiratory depression, pruritus, constipation) are similar among the different opioids, some side effects are due to accumulation of nonopioid metabolites that are unique to individual drugs. One striking example of this is normeperidine, a metabolite of meperidine. Normeperidine produces hyperexcitability and seizures that are not reversible with naloxone. Normeperidine accumulation is greater in patients with renal failure.

The most rapid relief with opioids is obtained by intravenous administration; relief with oral administration is significantly slower. *Common acute side effects include nausea, vomiting, and sedation. These effects are dose-related, and there is great variability among patients in the doses that relieve pain and produce side effects.* Because of this, initiation of therapy requires titration to optimal dose and interval. The most important principle is to provide adequate pain relief. This requires asking the patient whether the drug has relieved the pain and, if so, when the relief wears off. *The most common error made by physicians in managing severe pain with opioids is to prescribe an inadequate dose. Since many patients are reluctant to complain, this practice leads to needless suffering.* In the absence of sedation at the expected time of peak effect, a physician should not hesitate to repeat the initial dose to achieve satisfactory pain relief.

An innovative approach to the problem of achieving adequate pain relief is the use of patient-controlled analgesia (PCA). PCA requires a device that immediately delivers a pre-programmed dose of an opioid drug when the patient pushes a button. The device can be programmed to limit the total hourly dose so that overdosing is impossible. The patient can then titrate the dose to the optimal level. This approach is used most extensively for the management of postoperative pain, but there is no reason why it should not be used for any hospitalized patient with persistent severe pain. PCA is also used for home care of patients with intractable pain, such as metastatic cancer.

Table 12-1

Drugs for Relief of Pain

NONNARCOTIC ANALGESICS: USUAL DOSES AND INTERVALS

Generic Name	Dose, mg	Interval	Comments
Acetylsalicylic acid	650 PO	q 4 h	Enteric-coated preparations available
Acetaminophen	650 PO	q 4 h	Side effects uncommon
Ibuprofen	400 PO	q 4–6 h	Available without prescription
Naproxen	250–500 PO	q 12 h	Delayed effects may be due to long half-life
Fenoprofen	200 PO	q 4–6 h	pa
Indomethacin	25–50 PO	q 8 h	Gastrointestinal side effects common
Ketorolac	15–60 IM	q 4–6 h	Available for parenteral use (IM)

NARCOTIC ANALGESICS: USUAL DOSES AND INTERVALS

Generic Name	Parenteral Dose, mg	PO Dose, mg	Comments
Codeine	30–60 q 4 h	30–60 q 4 h	Nausea common
Oxycodone	—	5–10 q 4–6 h	Usually available with acetaminophen or aspirin
Morphine	10 q 4 h	60 q 4 h	
Morphine sustained release	pa	60–180 bid to tid	Oral slow-release preparation
Hydromorphone	1–2 q 4 h	2–4 q 4 h	Shorter acting than morphine sulfate
Levorphanol	2 q 6–8 h	4 q 6–8 h	Longer acting than morphine sulfate; absorbed well PO
Methadone	10 q 6–8 h	20 q 6–8 h	Delayed sedation due to long half-life
Meperidine	75–100 q 3–4 h	300 q 4 h	Poorly absorbed PO; normeperidine a toxic metabolite
Butorphanol	—	1–2 q 4 h	Intranasal spray
Fentanyl	—	—	Transdermal patch

ANTICONVULSANTS AND ANTIARRHYTHMICS

Generic Name	PO Dose, mg	Interval
Phenytoin	300	daily/qhs
Carbamazepine	200–300	q 6 h
Clonazepam	1	q 6 h
Mexiletine	150–300	q 6–12 h

TRICYCLIC ANTIDEPRESSANTS

Generic Name	Uptake Blockade		Sedative Potency	Anticholinergic Potency	Orthostatic Hypotension	Cardiac Arrhythmia	Average Dose, mg/day	Range, mg/day
	5HT	NE						
Doxepin	++	+	High	Moderate	Moderate	Less	200	75–400
Amitriptyline	++++	++	High	Highest	Moderate	Yes	150	25–300
Imipramine	++++	++	Moderate	Moderate	High	Yes	200	75–400
Nortriptyline	+++	++	Moderate	Moderate	Low	Yes	100	40–150
Desipramine	+++	++++	Low	Low	Low	Yes	150	50–300

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The PHARMACOLOGICAL BASIS OF THERAPEUTICS

Joel G. Hardman
Lee E. Limbird

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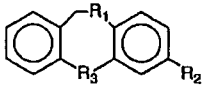
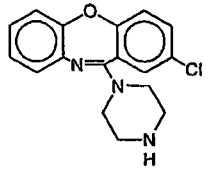
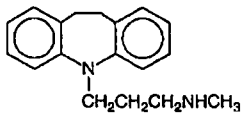
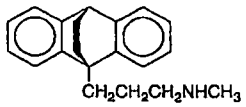
Table 19–1
Antidepressants: Chemical Structures, Dose and Dosage Forms, and Side Effects

NONPROPRIETARY NAME (TRADE NAME)	DOSE AND DOSAGE FORMS			SIDE EFFECTS						
	Usual Dose, mg/day	*Extreme Dose, mg/day*	*Dosage Form*	*Amine Effects*	*Sedation*	*Anti-cholinergic Effects*	*Hypo-tension*	*Cardiac Effects*	*Seizures*	*Weight Gain*
Norepinephrine-Reuptake Inhibitors: **Tertiary Amine Tricyclics**  R_1 R_2 R_3										
Amitriptyline (ELAVIL and others) C H $C{=}CH(CH_2)_2N(CH_3)_2$	100–200	25–300	O, I	NE, 5-HT	+++	+++	+++	+++	++	++
Clomipramine (ANAFRANIL) C Cl $N{-}(CH_2)_3N(CH_3)_2$	100–200	25–250	O	NE, 5-HT	++	+++	++	+++	+++	+
Doxepin (ADAPIN, SINEQUAN) O H $N{=}CH(CH_2)_2N(CH_3)_2$	100–200	25–300	O	NE, 5-HT	+++	++	+++	++	++	++
Imipramine (TOFRANIL and others) C H $N{-}(CH_2)_3N(CH_3)_2$	100–200	25–300	O, I	NE, 5-HT	++	++	++	+++	++	++
(+)-Trimipramine (SURMONTIL) C H $N{-}CH_2CH(CH_3)CH_2N(CH_3)_2$	75–200	25–300	O	NE, 5-HT	+++	+++	++	+++	++	++
Norepinephrine-Reuptake Inhibitors: **Secondary Amine Tricyclics**										
Amoxapine (ASENDIN) 	200–300	50–600	O	NE, DA	+	+	++	++	++	+
Desipramine (NORPRAMIN, PERTOFRANE) 	100–200	25–300	O	NE	0/+	+	+	++	+	+
Maprotiline (LUDIOMIL) 	100–150	25–225	O	NE	++	++	++	++	+++	+

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